REMARKS

Claims 1-12, 15-18, and 21-27 are currently pending in this application. Claims 14, 19, and 20 are cancelled with this amendment. New claims 25-27 are added. Support for the amendment to claim 1 and for new claims 25-27 appears in, e.g., paragraphs 5 and 48-49. No new matter has been added.

Applicants note that they submitted a Supplemental Information Disclosure for this application on September 25, 2009.

Rejections under 35 U.S.C. § 103(a)

Claims 1-5, 8, and 14-24 are rejected as unpatentable over US Patent No. 5,506,222 ("Stefano") in view of Mueller et al. and DrugBank (http://redpoll.pharmacy.ualberta.ca/drugbank) and of Mehnert at l. and zur Mtihlen et al. Claims 14, 19, and 20 are cancelled with this amendment. The rejection is traversed to the extent it is applied to the remaining claims as amended.

Obviousness is evaluated according to the test set forth in Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966) [see also KSR Int'l Co. v. Teleflex Inc., 550 U.S. ___, 127 S. Ct. 1727 (2007) (slip. op., p. 2)]:

> "Under 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *See* MPEP § 2143.01, citing *KSR International Co. v. Teleflex, Inc.*, 550 U.S. ____, 82 USPQ2d 1385, 1396 (2007). Furthermore, a statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the

teachings of the references. *See* MPEP § 2143.01, citing *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

Combining references to produce spironolactone particles required by the claims was not predictable in view of the prior art. Independent claims 1, 21, and 22, from which the remaining claims subject to the rejection depend, have been amended to specify that the recited nanoparticle is stable. Prior to Applicants' invention, it was thought the spironolactone formulations would aggregate and flocculate over time. Paragraph 5 of the specification recites:

> [M]icroparticles and nanoparticles have a tendency to aggregate and flocculate, which has adverse consequences for the stability of the product A number of different approaches have been investigated for the preparation of microparticles and nanoparticles.

To respond to this need, Applicants developed spironolactone formulation method that produces stable particles useful for topical application. The specification explains in paragraph 18 that the stability of the claimed nanoparticle is an unexpected feature of the invention:

> Generally one would expect a noticeable increase in particle size on storage following the incorporation of very fine solid particles into a matrix which contains hydrophilic as well as lipophilic structures. Surprisingly, this did not happen and there was no noticeable crystal growth of Spironolactone over a seven month period. Furthermore, the cream has shown an increased flux rate in a membrane model with respect to a cream with non-nanoparticulate spironolactone.

The teachings of the specification teach how to make the stable spironolactone formulations according to the invention. The stability compared to prior art spironolactone formulations is illustrated in Example 2 and accompanying FIG. 2 (compare FIGS. 1 and 3).

The references cited by the Examiner do not lead to the claimed invention. As noted by the Examiner, Stefano is silent regarding oriented crystalline nanoparticles. Stefano focused on adding penetration enhancers to a topical spironolactone formulation to increase drug availability (see, e.g., col. 3, lines 51-58). There is no teaching or suggestion in this reference, however, of the stable spironolacatones now required by the claims.

Mueller is cited for teaching solid lipid nanoparticles of 50-1000 nm. This reference does not mention sprionolactones and fails to provide a teaching or suggestion for making a spironolactone nanoparticle that is stable and in the size range required by the claims.

Because the combination of references does not make obvious the claimed invention, Applicants request reconsideration and withdrawal of the rejections of claims 1-5, 8, and 15-28, and 20-24 for obviousness.

Claims 3-5 are rejected as unpatentable over Stefano in view of Mueller, and further in view of Sojoblom (Emulsions-a fundamental and practical approach, pages 64-65, 1992, Kluwer Academic Publishers). The rejection is traversed to the extent it is applied to the claims as amended.

Claims 3-5 depend directly or indirectly from claim 1 and are non-obvious over the combination of Stefano and Mueller for the reasons given above. Sojoblom is cited for teaching lipids with a crystallization temperature in the range recited in claims 3-5. This reference, however, does not supply a teaching that remedies the deficiencies of Stefano and Mueller.

Claims 6, 7 and 9-12 are rejected as unpatentable over Stefano in view of Mueller and further in view of Hansen, US Patent No. 6,228,383 B1 and Klein, US Patent No. 6,013,637. The rejection is traversed to the extent it is applied to the claims as amended.

Claims 6, 7, and 9-12 depend directly or indirectly from claim 1 and are non-obvious over the combination of Stefano and Mueller for the reasons given above. Hansen and Klein are cited for teaching lipids with a crystallization temperature in the range recited in claims 3-5. Hansen is cited for teaching that lipid crystals are formed from polar liquids such as water and glycerol, that lipid crystals include glyceryl monoesters of C1-8 fatty acids. Klein is cited for teaching that sodium docusate is a stabilizing agent used in topical pharmaceuticals. These references, however, also fail to do not supply a teaching that remedies the deficiencies of Stefano and Mueller.

Accordingly, Applicants request reconsideration and withdrawal of the rejections for obviousness.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 15-18, 22, and 24 are rejected for overbreadth. The rejection is traversed to the extent it is applied to the claims as amended.

The Examiner acknowledges that the specification is enabling for a method of treating acne, hirsutism, androgenic alopecia and rosacea. While not agreeing with this position, to expedite prosecution Applicants have amended claims 18 and 22, from which depend the remaining claims subject to the rejection, to specify these conditions. Accordingly, the rejection can be withdrawn.

Applicants submit that the application is in condition for allowance and request an action for same. A petition for extension of time accompanies this response. Please charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 28069-608N01US.

Respectfully submitted,

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